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Technical paper

Non-physiological antioxidants: How safe?

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Abstract

Antioxidants of various origins, by these days are one of the known health promotion tools in the world. These are also vastly used as over-the-counter medications. Having a protective capacity, antioxidants have been procured much attention in various fields; these include- dietary consumption, medicinal and cosmetic preparations, food and drinks preparation and preservation, and so on. Antioxidants are more concerned with the medical and pharmaceutical fields, where therapeutic applications are the prime apprehension. Our body has a number of antioxidants called physiological antioxidant systems. Generally, antioxidants are the reducing agents. A failure of balance between the production of oxidative substances and internal or physiological antioxidant molecules asks us to intake external or non-physiological antioxidants. How safe the non-physiological antioxidants? This text sketches theoretically a short scenario on safety and precautions of biologically installation of non-physiological antioxidants. This article is an update of previously published article by EC Orthopaedics 5.2 (2017): 29-31, where the author reserves all rights.

Keywords: *Non-Physiologic Antioxidants; Oxidative Stress; Precautions.*

1. Introduction

Reduction-oxidation reaction, collectively known as 'redox reaction' is important for biological cell function. Nonetheless, thousands of redox events are occurring in our body in a moment. To date, a number of events have been depicted. In this regard, reactive species play a pivotal role. Among the reactive species, reactive oxygen and nitrogen (ROS/RNS) are vastly studied for their patho-physiological contributions (Kamata and Hirata 1999), despite of other oxidizable substances, including metal ion, atoms, molecules, radicals; intermediates etc. are also should be included in this family.

The sources of oxidizable substances are numerous. At normal level, their functions are necessary, especially for physiological functions, immunological defense, killing of pathogens, induction of some essential chronic low level inflammatory actions, and so on. An excess of them creates etiology of numerous pathology, which may accelerate or stimulate some disease states, and cause diseases by destruction of cell membrane, interfering cellular function, damaging of cell macromolecules such as carbohydrates, proteins, lipids or even genetic materials (e.g. – DNA, RNA). However, we have a number of natural antioxidant systems in our body such as catalase (CAT), superoxide dismutase (SOD), and glutathione (i.e. – peroxidase, S-transferase, reduced) (Islam 2016). These are generally saving our body from oxidizable substances induced oxidative stress (a situation results in higher production of oxidizable substances than the antioxidant molecules). An over production of these oxidizable substances other than the physiological antioxidant molecules asks us to intake external antioxidants of various sources and formulations.

The non-physiological antioxidants may act through several pathways: (i) oxidize in the place of victim substances; (ii) reduce the oxidized substances and/or re-install their physiological roles; (iii) capture reactive species and scavenge from their site of action; (iv) stimulate physiological antioxidant and repair systems (both in active and delayed states); and (v) act synergistically with physiological antioxidant systems (Islam 2016).

To be mentioned that, antioxidants may act as pro-oxidants, generally the effect is called as 'protective effect'. This pro-oxidative effect is also a cytotoxic effect, which is attained at high concentration of an antioxidant. Certain vitamins such as vit A, C and E, some essential oils, especially the polyphenols are known to act as a pro-oxidant at high concentration (Islam 2016).

In general, the redox imbalance is the main cause of long-term stay of oxidation or reduction states. Each of this state may disturb other stable conditions due to their capability to exert stress on them. The events generally termed as a cyclic or chain reaction. Biological responses are interconnected to each other. A change in one terminal may influence to others. It is not only for escaping the necessary oxidizable substances, but also for the avoidance of antioxidant-mediated 'antioxidative stress'. Otherwise, regular usages of non-physiological antioxidants may attain a dependency, especially to the function of physiological repairing and antioxidant systems, which are thought to be stimulated by these external antioxidants. Notably, neutralization of required reactive species for normal physiological functions, may lead to progression of cancer or delay aging (Poljsak and Milisav 2012). Moreover, the compatibility and site specificity in non-physiological antioxidant therapy are two major concerns. Is it possible to reach for an antioxidant to all the oxidative stress sites of a biological system and act effectively? The site-specific polarity of a biological system and the type of oxidant to be neutralized may restrict their activity. There is no doubt, that antioxidant therapy may reduce the power of some vital biological events such as immunological defense, essential low-levels of inflammatory action, those are related to the oxidizable substances. Otherwise, in some cases, antioxidants may not bring fruitful results as protective agents. For an example - antioxidant therapy with antineoplastic drugs, in this regard, if antioxidant is used prior to the antineoplastic drug, not only the

normal cells, it will protect the cancer cells also. As a co-treatment, it may reduce the efficacy of the antineoplastic drug, while as a post-treatment, it may stimulate the biological repair system, thus the cancer regain. In all cases, there is a chance of escaping of cancer cells. An antioxidant, in this context acts as an antagonist of the chemotherapeutic agent, as most of chemotherapeutic agents act by chronic reactive species induction pathway (Gupta et al. 2012).

How necessary of a pro-oxidative effect, especially when a biological system is in homeostasis? This type of effect is welcome in the case of pathogenic attack and for the destruction of malfunctioning or cancerous cells from the body. Thus, cells having set infrastructure with normal physiological functions are not in an agreement with this effect. Otherwise, our daily diets are also supplying some non-physiological antioxidants (directly or indirectly). An antioxidative stress may trigger not only a delayed oxidation state, but also maintains a long-term, reducing effects on the cells, which is also another cause of aging (Yang et al. 2007). In fact, redox homeostasis is essential for cell self-renewal (Chatoo et al. 2009; Liu et al. 2009) as well as in genomic stability (Li and Marban 2010). Some important events in a biological cell of an antioxidant have been shown in Fig 1. Furthermore, pro-oxidative ROS can induce apoptosis and necrosis by several pathways as shown in Fig 2.

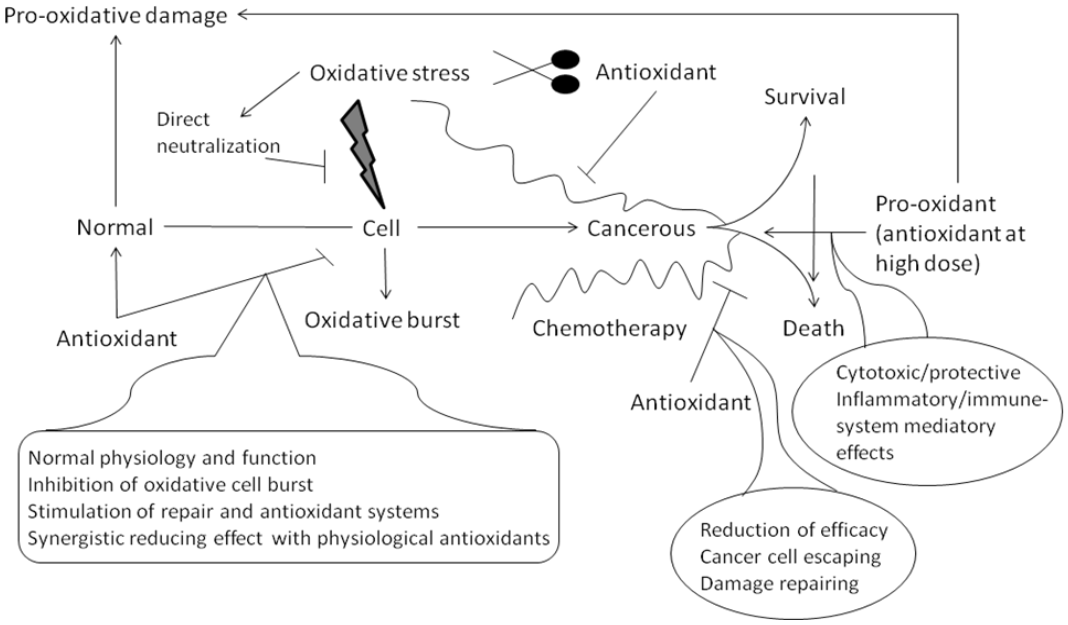

Fig. 1: Oxidative-Stress-Induced Events and Probable Antioxidant Functions in a Cell.

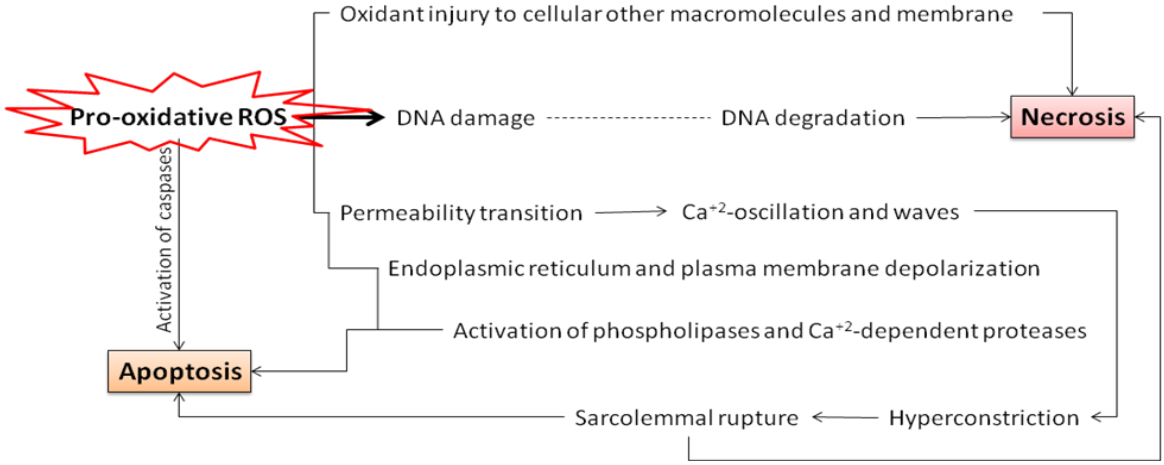

Fig. 2: In General, Pro-Oxidative ROS-Mediated Apoptosis and Necrosis.

ROS-mediated few other cellular detrimental events have been shown in Fig 3 and Fig 4.

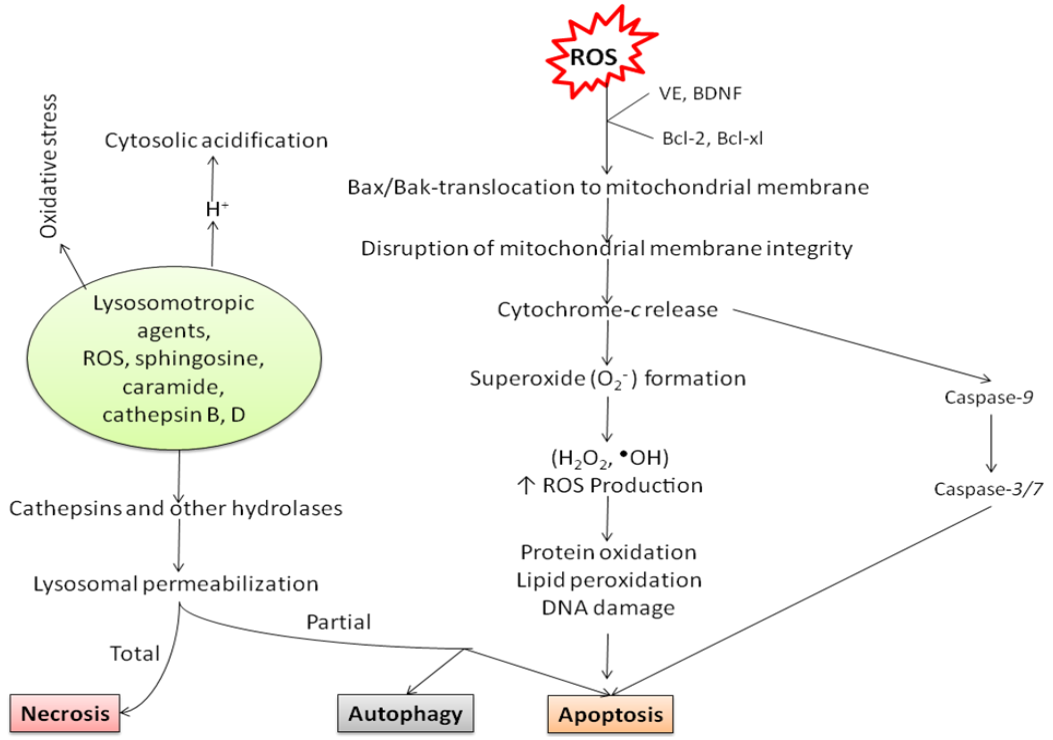

Fig. 3: ROS-Induced Necrosis, Autophagy and Apoptosis Events in Eukaryotic Cells. [BDNF: Brain-Derived Neurotrophic Factor; ROS: Reactive Oxygen Species; VE: Vascular Endothelium]

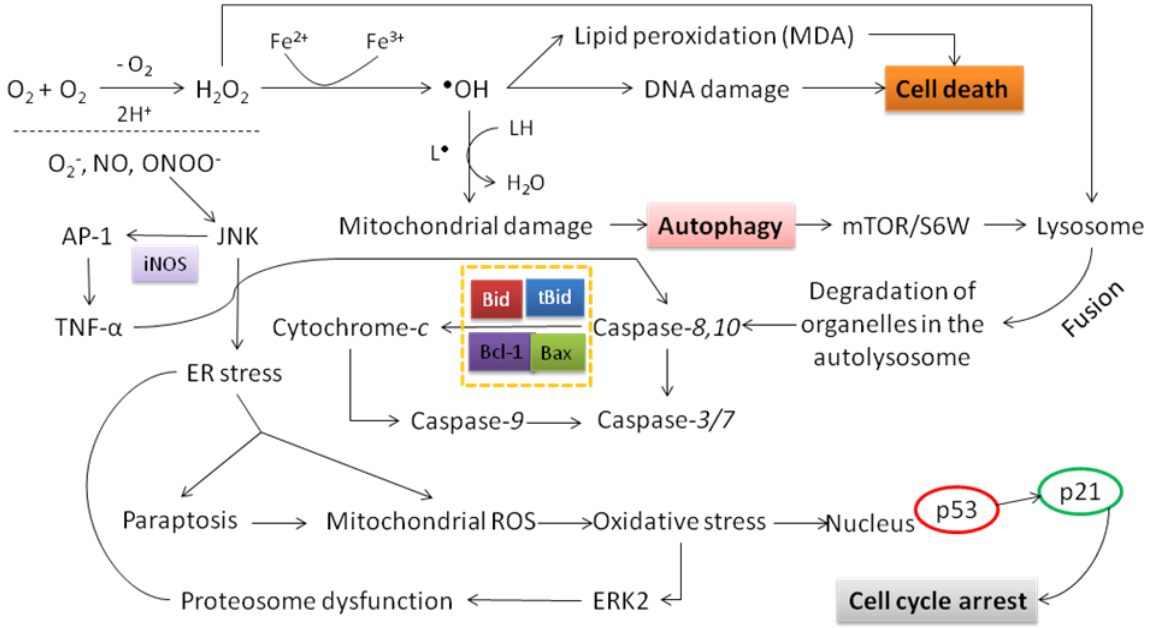

Fig. 4: ROS-Induced Cell Death and Cell-Cycle Arrest and Other Relevant Events. [AP-1: Activator Protein-1; ER: Endoplasmic Reticulum; ERK2: Extracellular Receptor Kinase 2; Inos: Inducible Nitric Oxide Synthase; JNK: C-Jun-N-Terminal Kinases; LH: Lipid Molecule; MDA: Malonylaldehyde; ROS: Reactive Oxygen Species; TNF-A: Tumor Necrosis Factor Alpha]

The possible physiological disagreements with an antioxidant therapy may be: (i) disturbance in homeostasis and cellular normal function; (ii) escaping cancer cells or induction of cancerous events; (iii) escaping pathogens; (iv) immunosuppressive effects; (v) severe inflammatory events; (vi) unnecessary or inadequate protection; (vii) prevention or over-stimulation of physiological antioxidant systems; (viii) antioxidant-mediated cell and cellular material damage; and (ix) dependency on non-physiological antioxidants.

Despite of cytoprotectivity, a number of artificial antioxidants are also evident to exert adverse effects on biological systems, which stimulates scientists to search natural antioxidants and a continuous basis work on antioxidants (Islam et al. 2016). Oxidative stress-mediated diseases are numerous. To date, over 100 diseases have been identified (Gutteridge 1993). Therefore, the use of antioxidant regardless of their sources and side effects should be continued. Upon going through the above circumstances, it can be recommended that, the determination of oxidation level is crucial prior to taking any antioxidant medication.

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